Spatial Embedding of fMRI for Investigating Local Coupling in Human Brain

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ABSTRACT

In this paper, we have investigated local spatial couplings in the human brain by applying nonlinear dynamical techniques on fMRI data. We have recorded BOLD-contrast echo-planar fMRI data along with high-resolution T1-weighted anatomical images from the resting brain of healthy human subjects and performed physiological correction on the functional data. The corrected data from resting subjects is spatially embedded into its phase space and the largest Lyapunov exponent of the resulting attractor is calculated and whole slice maps are obtained. In addition, we segment the high-resolution anatomical image and obtain a down sampled mask corresponding to gray and white matter, which is used to obtain mean indices of the exponents for both the tissues separately. The results show the existence of local couplings, its tissue specificity (more local coupling in gray matter than white matter) and dependence on the size of the neighborhood (larger the neighborhood, lesser the coupling). We believe that these techniques capture the information of a nonlinear and evolving system like the brain that may not be evident from static linear methods. The results show that there is evidence of spatio-temporal chaos in the brain, which is a significant finding hitherto not reported in literature to the best of our knowledge. We try to interpret our results from healthy resting subjects based on our knowledge of the native low frequency fluctuations in the resting brain and obtain a better understanding of the local spatial behavior of fMRI. This exploratory study has demonstrated the utility of nonlinear dynamical techniques like spatial embedding in analyzing fMRI data to gain meaningful insights into the working of human brain.

Keywords: Functional MRI, Nonlinear Dynamics, Spatial Embedding, Local Coupling, Baseline fMRI

INTRODUCTION

Functional connectivity between distinct anatomical regions of the brain in resting-state has been well studied using fMRI. Most studies employ linear methods (Biswal *et al*, 1995, 1997; Lowe *et al*, 1998; Cordes *et al*, 2000; Hampson *et al*, 2002), though there have been a few attempts to utilize the advantages that nonlinear methods offer (LaConte *et al*, 2003). However, we are not aware of studies in which functional connectivity of highly proximal anatomical regions (like a local neighborhood of a voxel) are investigated using fMRI. Even though there has been an EEG study claiming that highly localized correlations in the neocortical brain is less compared to more global correlations in the adult brain (Srinivasan, 1999), the low spatial resolution of EEG is not ideal for spatially localized studies. Given the excellent spatial resolution that fMRI offers, it seems to be a better choice for studying spatially local coupling in the human brain.

The couplings in the local neighborhood of a voxel depend on the complex inter-relationships between neuronal activity, oxygen metabolism and hemodynamic response in that neighborhood. Since there is a lack of a specific BOLD response in resting-state, we can characterize the baseline local coupling. This baseline local coupling is likely to change during activation and pathology due to the fact that the inter-relations are likely to change. When we consider only the time evolution of a single voxel, we are essentially limited by the disadvantages of univariate analysis. On the other hand, when we probe the connectivity between anatomically distinct regions or larger neighborhoods, we are essentially relying on time synchrony in the signal as a measure of functional connectivity (Friston, 1993). Neither of the above methods satisfactorily reflect the changes in the coupling of local hemodynamic factors, which are critical parameters contributing to the fMRI signal.

Studies in the past have indicated at the nonlinear nature of BOLD response (Vasquez *et al*, 1998) and the existence of nonlinear coupling between the hemodynamic factors (Sameer *et al*, 2004). This is likely to introduce nonlinearity in the local couplings that we are trying to characterize and hence the use of nonlinear methods seems to be more prudent. Also, to capture the coupling in the local neighborhood, we would need a spatially multivariate method. The technique

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of spatial embedding seems to be a good choice for the kind of requirements we have. By estimating the Lyapunov exponents from the spatially embedded data (Gonzalez *et al*, 2000), we can get an estimate of the coupling in the local neighborhood. The utility of spatial embedding has been debated in literature, for example in the estimation of correlation dimension of EEG (Pritchard *et al*, 1996, 1999; Pezard *et al*, 1999), but nevertheless its utility has been demonstrated in the analysis of schizophrenic patients using EEG (Lee *et al*, 2001). Moreover the formulation by Gonzalez is very general in nature and presents itself nicely for application to fMRI data.

In the current study, we consider baseline fMRI to test our model and calculate parameters from the model which would yield information regarding brain physiology. The resting-state fluctuations in fMRI and its associated couplings have been an active area of research, of late, owing to the fact that due to the lack of a task-related BOLD response, the signal seems very complicated. The low frequency fluctuations in baseline fMRI are thought to carry vital physiological information and are important in functional connectivity (Biswal *et al*, 1995; Peltier *et al*, 2000). Several recent studies have shown decreased baseline low frequency correlations for patients in pathological states, including cocaine use (Li *et al*, 2000), cerebral lesions (Quigley *et al*, 2001), Tourette syndrome (Biswal *et al*, 1998), multiple sclerosis (Lowe *et al*, 2002) and Alzheimer's disease (Li *et al*, 2002). Therefore, the study of baseline fMRI is important not only from a methodological development point of view, but also clinically.

THEORY AND METHODS

This section provides a theoretical background and discusses the materials and methods used in this work. The first sub-section discusses the formulation of a spatio-temporal model for fMRI. The second sub-section elaborates on the fMRI data acquisition methods and subsequent analysis of the data.

1. A Spatio-temporal Model for fMRI

Even though we have a broad understanding of low dimensional chaotic systems (Kantz *et al*, 1997), very few studies treats high dimensional, spatially extended systems. In fact, in such systems there is a complex interplay between local dynamics and spatial interactions, which results in the phenomenon of spatio-temporal chaos (Gonzalez *et al*, 2000). In such cases, the system exhibits temporal chaotic evolution along with additional decay of spatial correlations. One can define both spatial and temporal Lyapunov exponents owing to instabilities exhibited in both space translations and time evolution. It is possible to obtain spatio-temporal chaos simply by spatially coupling low dimensional chaotic units.

Spatio-temporal systems have a spatial extent which may be continuous or discrete (Gonzalez *et al*, 2000). Continuous systems are typically modeled by partial differential equations whereas discrete systems employ ordinary differential equations (also called lattice differential equations). In the latter case, the system is considered as a collection of low dimensional dynamical systems coupled together by some spatial rule (Bunimovich, 1995). There exists a third category of extended dynamical systems where both space and time are discrete. Here the low dimensional maps are arranged in some discrete lattice configuration (Kaneko, 1984) resulting in the so called coupled map lattices (CMLs).

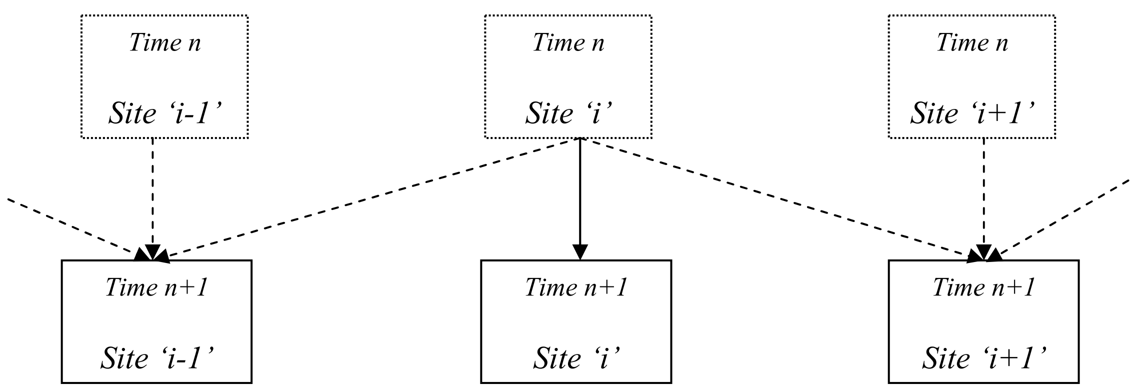

Figure.1 *A Coupled map lattice model used to describe the spatio-temporal dynamics of fMRI*

We would like to hypothesize the CML model shown in Fig. 1 to represent the spatio-temporal dynamics of fMRI. Using univariate temporal embedding we have recently shown that there is evidence of temporal chaos in fMRI (Deshpande *et al*, 2005) with a dimension of around ten. Therefore our spatio-temporal model of fMRI comprising a lattice of low dimensional units spatially coupled to each other is intuitively appealing.

The spatio-temporal dynamics of fMRI corresponding to the above model was reconstructed using spatial embedding and Lyapunov exponents were calculated (Geist *et al*, 1990, Von Bremen *et al*, 1997) from the spatially embedded attractor as an estimate of the amount of spatial coupling in the neighborhood of the voxel. Let us consider the general formulation of spatio-temporal embedding as shown in Eq.1 below,

$$y^n = (\varphi^n_j, \varphi^n_{j-1}, \ldots\ldots \varphi^n_{j-(ds-1)}) \tag{1}$$

whose entries $\varphi^n_j = (x^n_j, x^{n-1}_j, \ldots\ldots x^{n-(dt-1)}_j)$ are time delay vectors and spatial index j is fixed (Gonzalez *et al*, 2000) . If d_s and d_t denote the spatial and temporal embedding dimensions respectively, then the overall embedding dimension for such a spatio-temporal reconstruction is $d = d_s d_t$. By setting $d_s=1$, we get the standard temporal delay reconstruction (Takens, 1980). The addition of extra spatial delay in the time series enables the inclusion of important information which would have been very difficult to obtain otherwise. It has been shown for a simulated CML that a pure spatial reconstruction (with $d_t=1$ in Eq.1) gives the optimal result (Gonzalez *et al*, 1999, 2000; Orstavik *et al*, 1998). However, there is a need to incorporate time components ($d_t>1$) in order to obtain reasonable reconstructions in a more general scenario where the observables are nontrivial functions of the dynamical variables. Since we are computing the Lyapunov exponents in a local neighborhood of a voxel, we assume that the fMRI time-series represent a trivial transformation of the underlying dynamical variables corresponding to the physiological processes producing fMRI. Therefore a pure spatial embedding is employed as the method of choice in this work. However, if one were to reconstruct the joint dynamics of distant anatomical regions, then a spatio-temporal delay reconstruction would be more appropriate.

2. fMRI Data Acquisition and Analysis

Echo Planar Imaging (EPI) data were acquired from four healthy volunteers in resting state. The data was obtained on a 3T Siemens Trio (TR=750 ms, TE=35 ms, Flip Angle=50 deg and FOV=22cm, with 5 axial slices, 5mm slice thickness, 1120 images with 64 phase and frequency encoding steps). A physiological monitoring unit consisting of a pulse-oximeter and nasal respiratory cannula was used during data acquisition to record cardiac and respiratory signals, respectively. These physiological fluctuations were corrected in the functional data retrospectively (Hu *et al*, 1995). High resolution (512x512) T1-weighted anatomical images were acquired simultaneously, which was segmented automatically into gray matter and white matter. The resulting segmented image was down-sampled by a factor of 8 to get a 64x64 mask of gray matter and white matter. The spatial largest Lyapunov exponent (SLLE) is calculated by spatially embedding each voxel time-series with time series from a 5x5, 9x9 and 13x13 neighborhood. SLLE is an index of the spatial coupling in the local neighborhood of the voxel under consideration. A higher value of SLLE would indicate higher divergence of the local orbits in the attractor and hence less coupling between the individual dynamical units hypothesized to be represented by the voxels. The SLLE for each voxel of the slice is mapped as an image. Also, the mean values of SLLE are calculated for the gray and white matter masks, which gives one mean SLLE index for gray and white matter respectively.

RESULTS AND DISCUSSION

The top three rows of Fig. 2 show the SLLE maps for the three subjects. The last row shows a sample sagittal map for one of the subjects. The columns from left to right indicate the maps for 5x5, 9x9 and 13x13 neighborhoods. Tables 1(a), 1(b) and 1(c) tabulate the mean SLLE and correlation values for 5x5, 9x9 and 13x13 neighborhoods respectively. The relatively low positive values of SLLE clearly show that local coupling does exist in the brain. Given the fact that univariate temporal Lyapunov exponents are also a low positive value (Deshpande *et al*, 2005), we can infer that there is some evidence of spatio-temporal chaos in the brain. This is an important observation considering the fact that spatio-temporal chaos, a phenomenon observed in spatially extended natural systems has not been reported hitherto in the

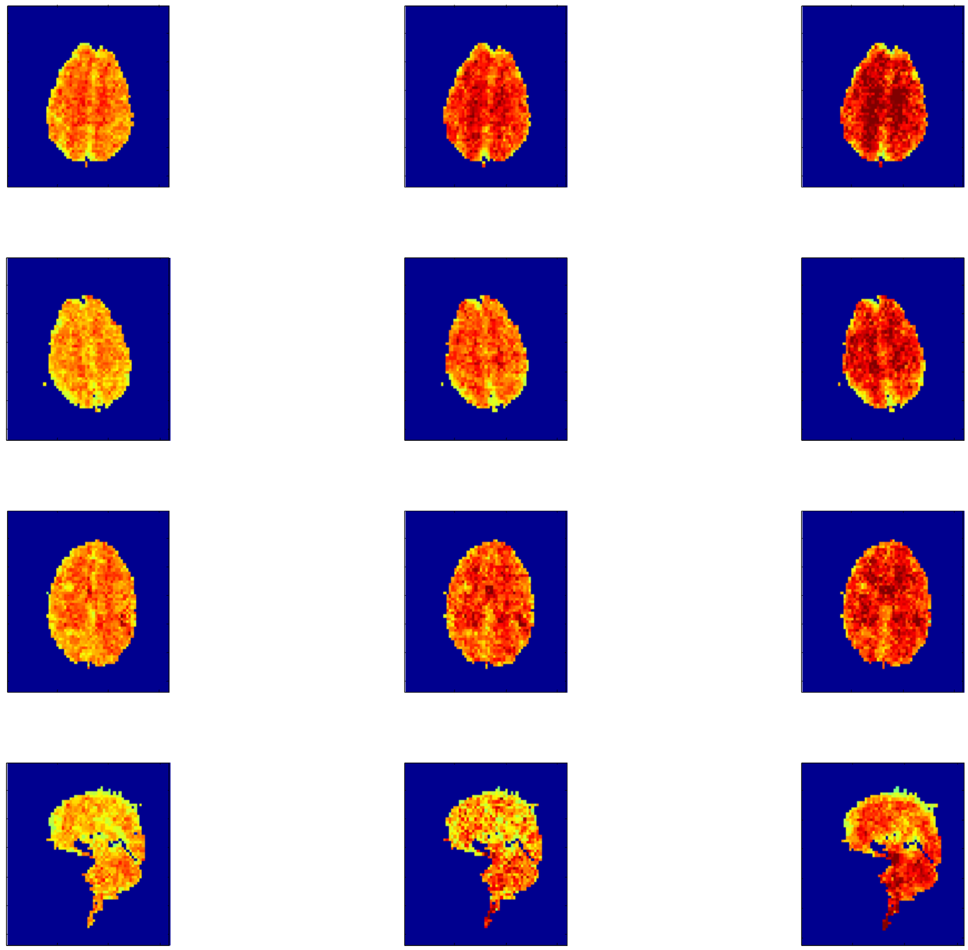

Figure 2. *Maps of SLLE. Top three rows are for the subjects 1, 2 and 3 respectively .The last row is the sagittal map for one of the subjects. Left to right represents 5x5, 9x9 and 13x13 neighborhoods respectively. Yellow- 0.6 and Red- 2*

brain to the best of our knowledge. Also, there is tissue specificity in the sense that gray matter exhibits more local coupling (less divergence) than white matter. The maps for the sagittal slice clearly show that local coupling in the cortex is much higher than in the sub-cortical areas. Comparison of the results for different neighborhoods suggest that with increasing size of the neighborhood the coupling is reduced, with the reduction being more rapid in white matter than in gray matter. Since we have already accounted for physiological fluctuations, the results can be interpreted in terms of the native fluctuations in the brain due to various factors like vasomotion, fluctuations in cerebral blood flow (CBF) and cerebral blood volume (CBV) and metabolic fluctuations including that of NADH (nicotinamide adenine dinucleotide) and HbO2 (oxyhemoglobin). These results render a new perspective into the local spatial couplings and behavior of these native phenomena in the brain using methods that would capture both the nonlinearity and dynamics of the system. Comparison of the results obtained by linear spatial correlation suggest that it also captures the same trend as that of SLLE, but the difference in the mean values for white and gray matter is higher for SLLE than for correlation. This may be attributed to the fact that SLLE accounts for both linear and nonlinear couplings and therefore is able to make a greater distinction between the processes in white and gray matter giving rise to the fMRI signal.

5x5	*SLLE*		*Linear Spatial Correlation*	
	Gray matter	*White matter*	*Gray matter*	*White matter*
Subject 1	*1.09*	*1.65*	*0.39*	*0.29*
Subject-2	*0.77*	*1.39*	*0.52*	*0.36*
Subject-3	*1.30*	*1.67*	*0.51*	*0.35*

Table 1(a). *Mean values of SLLE and linear spatial correlation for a 5x5 neighborhood*

9x9	*SLLE*		*Linear Spatial Correlation*	
	Gray matter	*White matter*	*Gray matter*	*White matter*
Subject 1	*1.23*	*1.84*	*0.38*	*0.29*
Subject-2	*0.87*	*1.57*	*0.50*	*0.35*
Subject-3	*1.59*	*1.88*	*0.50*	*0.34*

Table 1(b). *Mean values of SLLE and linear spatial correlation for a 9x9 neighborhood*

13x13	*SLLE*		*Linear Spatial Correlation*	
	Gray matter	*White matter*	*Gray matter*	*White matter*
Subject 1	*1.30*	*1.96*	*0.37*	*0.28*
Subject-2	*0.93*	*1.68*	*0.49*	*0.34*
Subject-3	*1.69*	*1.99*	*0.48*	*0.34*

Table 1(c). *Mean values of SLLE and linear spatial correlation for a 13x13 neighborhood*

CONCLUSIONS

In this study, we have investigated local spatial couplings in the human brain using fMRI and nonlinear dynamical techniques in resting healthy individuals. We have shown the existence of local couplings, its tissue specificity and dependence on the size of the neighborhood. We believe that our techniques capture the information of a nonlinear and evolving system like the brain that may not be evident in some other static linear methods. It has been shown that there is evidence of spatio-temporal chaos in the brain, which is a significant finding hitherto not reported in literature to the best of our knowledge. We have interpreted our results from healthy resting subjects based on what we know about the native low frequency fluctuations in the resting brain and obtained a better understanding of the local spatial behavior of fMRI. This study has demonstrated the utility of nonlinear dynamical techniques like spatial embedding in analyzing fMRI data to gain meaningful insights into the working of the human brain.

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